REMARKS

Claims 172, 175-181, 183-186, and 191-194 are currently pending and presented for examination. Applicants have hereinabove cancelled claims 187-190 without prejudice or disclaimer to applicants' right to pursue the subject matter of these claims in the future.

In addition, applicants have hereinabove amended claims 172, 175-181, 183-186, and 191-193. Support for amended claim 172 can be found *inter alia* in the description as filed at page 4, lines 19-23, page 4, line 31 to page 5, line 3, and page 16, lines 13-16. Support for amended claims 175-179 can be found *inter alia* in the description as filed at page 18, line 30 and page 19, line 8 and lines 19-21. Support for amended claim 180 can be found *inter alia* in the description as filed at page 35, lines 21-28. Support for amended claim 181 can be found *inter alia* in the description as filed at page 34, lines 9-13. Support for amended claim 183 can be found *inter alia* in the description as filed at page 35, lines 11-12. Support for amended claim 184 can be found *inter alia* in the description as filed at page 17, lines 28-32. Support for amended claims 185-186 can be found *inter alia* in the description as filed at page 35, line 19-28. Support for amended claim 191 can be found *inter alia* in the description as filed at page 18, line 30 and page 19, line 8 and lines 19-21. Support for amended claim 192 can be found *inter alia* in the description as filed at page 18, lines 10-17. Support for amended claim 193 can be found *inter alia* in the description as filed at page 4, lines 25-29; page 12, lines 11 and 12; page 18, lines 4-7; page 19, lines 6-8; and page 39, line 4 to page 41, line 10.

Applicants submit that amended claims 172, 175-181, 183-186, and 191-193 introduce no new subject matter and are fully supported by the application as originally filed.

Rejection Under 35 U.S.C. §112 - Enablement

In the September 29, 2009 Office Action, the Examiner alleged that the specification fails to enable the invention defined in claims 172, 175-181 and 183-194. The Examiner acknowledged that the specification enables a method of inducing neovascularization at a site of administration by administering mesenchymal precursor cells (MPCs) derived from bone marrow that express STRO-1. However, the Examiner asserted that it is unpredictable to extrapolate from the enabled subject matter to the repair of blood vessels in any tissue by administration of any STRO-1$^+$ cells from any source by any routes of administration.

Applicants' Response

Applicants respectfully traverse this rejection. Applicants submit that claim 172, as amended herein, recites "A method of inducing formation or repair of blood vessels in a first tissue in need of blood vessel formation or blood vessel repair, comprising contacting the first tissue with a population of cells enriched for mesenchymal precursor cells (MPCs) that express the marker STRO-1 or cultured or expanded cells derived therefrom, so as to thereby generate new blood vessels or to repair existing blood vessels in the first tissue." Applicants further submit the specification demonstrates that STRO-1 expressing cells from bone marrow, dental pulp, and adipose tissue are capable of differentiating into a variety of tissues such as bone, fat, cartilage and vascular tissues e.g. arterioles and other blood vessels, as indicated on page 17, lines 9-11; page 36, lines 14-16; page 38, lines 8-14 and page 39, line 1 to page 41, line 9. Hence, MPCs expressing STRO-1 can be isolated from non-bone marrow sources and share the same capability as bone marrow derived MPCs to differentiate into numerous tissue types *in vitro* (see Example 3, pages 35-38).

As the Examiner has acknowledged, the specification clearly exemplifies the administration of STRO-1 expressing MPCs isolated from bone marrow to tissues to induce production/repair of blood vessels *in vivo*, e.g., at page 39, line 1 to page 41, line 9. Accordingly, it is reasonable that STRO-1 expressing MPCs isolated from other tissue sources, which show similar *in vitro* properties to bone-marrow derived STRO-1 expressing MPCs, will also induce production/repair of blood vessels *in vivo*. The Examiner has not offered any evidence as to why this would not be the case.

Furthermore, with regard to the Examiner's comment that the specification does not enable "any routes of administration", applicants' note that the claims require that the tissue in need of blood vessel formation or repair is contacted with the STRO-1 expressing MPCs. Thus, the claims require contact of the target tissue with the MPCs and are adequately enabled.

Based on the foregoing, applicants maintain that one skilled in the art, in light of specification, would be able to perform the claimed method without undue experimentation. Accordingly, applicants maintain that the invention as claimed is enabled and respectfully request the Examiner to reconsider and withdraw this rejection.

Rejection Under 35 U.S.C. §103 - Obviousness

The Examiner asserted that claims 172, 175-181 and 183-191 were obvious over the combined teachings of Chopp et al., *The Lancet Neurology* 1:92-100, in view of Jones et al., *Arthritis and Rheumatism*, 46: 3349-3360, 2002, Bianco et al., *Stem Cells* 19: 180-192, and Dennis et al., *Cells Tissues Organs*, 170: 73-82.

In particular, the Examiner asserted that Chopp et al. discloses methods that result in angiogenesis or vasculogenesis following treatment of a neural injury with bone marrow stromal cells including mesenchymal stem cells (MSCs). The Examiner also equates MSCs with Mesenchymal Precursor Cells (MPCs). The Examiner based this rejection on the notion that the disclosure in Chopp et al. illustrates that MSCs inherently express STRO-1 and that this was known at the time of the instant invention. The Examiner does not provide support for this assertion.

The Examiner does acknowledge that Chopp et al. does not teach the various claimed markers on said MSCs. However, on page 7 of the Office Action the Examiner states: "Thus, it would have been obvious for one of ordinary skill in the art to incorporate into the method of promoting angiogenesis in an organ or tissue by administering MSCs/MPC as taught by Chopp with a step of confirming the identity of MSCs or MPCs as STRO-1+ or STRO-1^{bright} cells and enriching them as taught by Jones et al. and/or Bianco et al." The Examiner also asserted it would have been obvious "to administer an effective amount of STRO-1^{bright} cell enriched MPCs to induce neovascularisation in a tissue as Dennis teaches that they can differentiate into vascular smooth muscle cell and endothelial cell phenotype."

Applicants' Response

Applicants respectfully traverse this rejection. Applicants note that the Examiner continues to assert that the MSCs described by Chopp et al. are in fact Mesenchymal Precursor Cells (MPCs). The Examiner has not addressed the issue that MPCs are not co-extensive with "bone-marrow stromal cells" ("MSCs") of Chopp et al.

In addition, Chopp et al. describes the MSCs as "uncharacterized." Accordingly, it is not clear which cells of the MSCs described by Chopp et al. are responsible for the effects seen by Chopp et al. Chopp et al. does not suggest the cells responsible for vasculogenesis are MPCs. Applicants also note that the MSCs described in Chopp et al. are isolated by a technique which involves adherence of the cells to a plastic dish (see Chopp et al. on page 93, left hand column). In contrast, the MPCs of the present application were isolated using immunoselection. It is not surprising therefore, that the MSCs referred to by Chopp et al. are substantially different to the MPCs of the present invention. In addition, as shown in Table 1 of the present application, mesenchymal stem cells do not express detectable levels of STRO-1. Applicants maintain that the MSCs described by Chopp et al. are not relevant to the present claims because they are not STRO-1$^+$ MPCs and are not a "population of cells enriched for mesenchymal precursor cells (MPCs) that express the marker STRO-1 or cultured or expanded cells derived therefrom."

Applicants also note that Jones et al. discloses the characterization of a population of mesenchymal progenitor cells (MPCs) (not a population of bone-marrow stromal cells described by Chopp et al.). In fact, at page 93, left hand column, bottom paragraph, Chopp et al. makes it clear that bone-marrow stromal cells are not co-extensive with mesenchymal progenitor cells. Because there is no teaching in Chopp et al. as to which subpopulation(s) of cells of the "uncharacterized" bone-marrow stromal cells disclosed therein is responsible for the vasculogenic effects observed, it is not reasonable to state that one skilled in the art would administer the bone-marrow stromal cells of Chopp et al. and then take the (unsuggested) step of confirming that the cells were STRO-1$^+$ based on Jones et al.

Moreover, administering the bone-marrow stromal cells of Chopp et

al. does not render obvious applicants' claimed method of administering a different enriched population of cells, i.e. STRO-1$^+$ mesenchymal precursor cells. Absent applicants' disclosure of the role of the STRO-1$^+$ MPCs in formation and repair of blood vessels, and absent hindsight reconstruction, why would one skilled in the art specifically enrich for STRO-1$^+$ MPCs and then administer them to effect neovascularization? There is no suggestion of such.

The Examiner has stated that one skilled in the art would be motivated to use STRO-1$^+$ cell enriched MPCs in order to induce angiogenesis as it "promotes healing of the affected organ by relieving ischemia." However, this is a logic jump which does not account for the motivation to use a population of cells enriched for STRO-1$^+$ mesenchymal precursor cells in the first instance. Moreover, there is no suggestion in the prior art to use this specific population to effect the formation and repair of blood vessels.

Applicants note therefore that the invention claimed is not rendered obvious by the primary reference of Chopp et al. in combination with the remaining references. However, applicants note that there are additional issues with the references of Jones el al., Bianco et al. and Dennis et al.

Claim 172, as amended herein, recites "A method of inducing formation or repair of blood vessels in a first tissue in need of blood vessel formation or blood vessel repair, comprising contacting the first tissue with a population of cells enriched for mesenchymal precursor cells (MPCs) that express the marker STRO-1 or cultured or expanded cells derived therefrom, so as to thereby generate new blood vessels or to repair existing blood vessels in the first tissue." However, Jones et al., Bianco et al., and Dennis et al. disclose STRO-1$^+$ cells but none of these references suggest that this specific population of cells are

capable of inducing blood vessel formation or repair.

Applicants note that the disclosure in Bianco et al. teaches that bone-marrow stromal cells are progenitors of skeletal tissue components such as bone, cartilage, the hematopoiesis-supporting stroma and adipocytes (see abstract). Applicants further note that the disclosure in Bianco et al. does not teach that the bone-marrow stromal cells are capable of differentiating into vascular cells. Instead, Bianco et al. merely demonstrates that the bone marrow stromal cells are potentially components of the vascular wall. There is no suggestion in Bianco et al. that the cells would be capable of differentiating into vascular cells or inducing blood vessel repair or formation.

Applicants note that Dennis et al. demonstrates that STRO-1$^+$ marrow cells are capable of differentiating into multiple mesenchymal lineages including hematopoiesis-supportive stromal cells with a vascular smooth muscle-like phenotype, adipocytes, osteoblasts and chondrocytes. Accordingly, the applicants respectfully disagree with the Examiner assertion that Dennis et al. teaches vascular differentiation potential of the STRO-1$^+$ fraction. In fact, applicants note that Dennis et al. teaches that STRO-1$^+$ cells are capable of differentiating into hematopoiesis-supportive stromal cells which have an appearance of "vascular smooth muscle-like cells," but are not vascular smooth muscle cells (see abstract, last sentence). There is no suggestion in Dennis et al. that the STRO-1$^+$ cells would be capable of differentiating into endothelial cells or that they would be capable of inducing blood vessel repair or formation.

Accordingly, applicants maintain that administration of the specific population of cells recited in claim 172 as amended is neither taught or suggested by, nor obvious over, the cited combination of art. Accordingly, respectfully requests that the Examiner reconsider and withdraw the instant rejection.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following items, which are listed on the substitute Form PTO-1449 attached hereto as **Exhibit A**. Copies of items 1-12 are attached hereto as **Exhibits 1-12,** respectively.

1. Yang XB, et al. (2006), "Evaluation of Human Bone Marrow Stromal Cell Growth on Biodegradable Polymer/Bioglass Composites," Biochemical And Biophysical Research Communications 342:1098-1107; **(Exhibit 1)**

2. Fujii, S. et al. (2008), "Investigating a Clonal Human Periodontal Ligament Progenitor/Stem Cell Line *In Vitro* and *In Vivo*," J. Cell. Physiol. 215:743-749; **(Exhibit 2)**

3. Neuhaus T. et al. (2003) "Stromal cell-derived factor 1alpha (SDF-1alpha) induces gene-expression of early growth response-1 (Egr-1) and VEGF in human arterial endothelial cells and enhances VEGF induced cell proliferation" Cell Proliferation. 36:75-86; **(Exhibit 3)**

4. Salcedo R. et al. (1999) "Vascular endothelial growth factor and basic fibroblast growth factor induce expression of CXCR4 on human endothelial cells: *In vivo* neovascularization induced by stromal-derived factor-1alpha" American Journal of Pathology. 154:1125-1135; **(Exhibit 4)**

5. Examination report issued October 10, 2009 in connection with European Application No. 05754008.0; **(Exhibit 5)**

6. Final Office Action issued June 22, 2009 in connection with U.S. Serial No. 10/551,162; **(Exhibit 6)**

7. Final Office Action issued June 23, 2009 in connection with U.S. Serial No. 11/169,875; **(Exhibit 7)**

8. Final Office Action issued July 16, 2009 in connection with U.S. Serial No. 10/955,709; **(Exhibit 8)**

9. Final Office Action issued October 08, 2009 in connection with U.S. Serial No. 11/326,736; **(Exhibit 9)**

10. Notice of Allowance issued October 29, 2009 in connection with U.S. Serial No. 10/813,747. **(Exhibit 10)**

11. Final Office Action issued Dec 09, 2009 in connection with U.S. Serial No. 11/169,875; **(Exhibit 11)**

12. Office Action issued January 19, 2010 in connection with corresponding Japanese Application No. 2006-503989. **(Exhibit 12)**

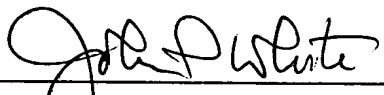
The Examiner is respectfully requested to make of record each item listed on Form PTO-1449 Substitute by initialing and dating the attached Form PTO-1449 Substitute, and returning a copy of the initialed and dated form to applicants' undersigned attorney.

This Supplemental Information Disclosure Statement is being submitted under 37 C.F.R. §1.97(b)(4), after the filing of a request for continued examination under 37 C.F.R. §1.113. Accordingly, no fee is required for filing this Supplemental Information Disclosure Statement.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the total enclosed $960.00, including $405.00 for filing a Request for Continued Examination and $555.00 for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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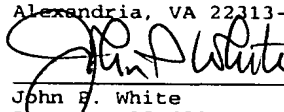

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